Skin care in chronic venous insufficiency

What should be considered from an allergological point of view?

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Keywords
Chronic venous insufficiency, skin care, contact allergy

Summary
Based on data of the Information Network of Departments of Dermatology (IVDK) of the years 2012–2016, we describe the spectrum of contact sensitization in 2 011 patients with venous ulcers, stasis dermatitis and/or chronic venous insufficiency (CVI) and compare it to the sensitization spectrum of an age-matched control group (n=30 924) without these diseases. CVI patients frequently were sensitized to balsam of Peru, ointment base ingredients, particularly lanolin alcohols, antioxidants, in particular tert-butylhydroquinone, colophony, fragrances, and parabens. Compared to earlier IVDK data analyses, the sensitization spectrum is qualitatively unchanged. Skin care products for CVI patients should not contain Balsam of Peru (Myroxylon pereirae), fragrances, lanolin alcohols, tert-butylhydroquinone (TBHQ), and parabens. It should be noted that there are the so-called paraben and lanolin paradoxes: CVI patients may have intolerance reactions to parabens or lanolin alcohols on eczematous skin at the lower leg, while at the same time tolerating these compounds on healthy, normal skin in other regions of the body.

Schlüsselwörter
Chronisch venöse Insuffizienz, Hautpflege, Kontaktallergie

Zusammenfassung
An Hand von Daten des Informationsverbundes Dermatologischer Kliniken (IVDK) der Jahre 2012–2016 wird das Spektrum von Kontaktsensibilisierungen bei 2 011 Patienten mit Ulcus cruris venosum, Stauungsekzem und/oder einem Kontaktekzem bei chronisch venöser Insuffizienz (CVI) beschrieben, und mit dem Sensibilisierungsspektrum einer Kontrollgruppe (n=30 924) im ähnlichen Alter, aber ohne diese Erkrankungen verglichen. Unverändert zu früheren IVDK-Auswertungen zeigten CVI Patienten gehäuft Sensibilisierungen gegen das folgende Allergenspektrum: Perubalsam, Bestandteile von Salbengrundlagen, insbesondere Wollwachsalkohole, Antioxidantien, insbesondere tert-Butylhydrochinon, Kolophonium, Duftstoffe und Parabene. Für die Hautpflege bei entsprechenden Patienten empfehlen sich daher duftstoff- und parabenfreie Produkte ohne Perubalsam (Myroxylon pereirae), Wollwachsalkohole (Lanolin alcohol) und tert-Butylhydrochinon (TBHQ). Dabei ist das sogenannte Paraben- und Wollwachs-Paradox zu berücksichtigen: CVI Patienten können an ekzematös veränderter Haut am Unterschenkel auf Parabene oder Wollwachsalkohole reagieren, während diese Stoffe auf normaler Haut an anderen Körperregionen vertragen werden.

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Introduction

Although skin care products in general can certainly not be counted as some of the things that cause epidermal sensitisation particularly often, the risk of sensitisation is likely to be increased in chronic venous insufficiency (CVI), especially in areas where the skin is inflamed, as a result of the damaged epidermal barrier and/or specific immunological conditions (1, 2). Preservatives, fragrances, ointment base constituents, emulsifiers or other excipients can act as potential allergens in relevant products (3, 4).

Based on the data collected by the Information Network of Departments of Dermatology (IVDK), in this paper we describe the sensitisation spectrum of patients with CVI, point out special features and from them derive advice for everyday practice.

Material and methods

The IVDK is a network of currently 56 dermatology departments in Germany, Switzerland and Austria that is investigating the clinical epidemiology of contact allergy. After obtaining informed consent, the medical history and clinical data of all patients undergoing patch testing at the participating centres, together with the patch test results, are stored in local databases. Every six months, these data are sent in pseudononymised form to the central IVDK office, which is an affiliated institute of the Faculty of Medicine at Göttingen University. There the data are subjected to quality control and are then added to the central IVDK database. The IVDK has the largest such database in the world, with datasets of approx. 275,000 patients (5).

All IVDK members carry out the patch tests according to the guidelines of the German Contact Dermatitis Research Group (DKG) (6). Test reactions on Day 3 were used for the present data evaluation. In a few cases, results were not recorded on Day 3, but on Day 4, and these were then used for the evaluation. All reactions with erythema with erythema, infiltration, papules and/or vesicles were assessed as positive, and coded as +, ++, or +++. The test preparations were obtained from SmartPractice Europe. Finn Chambers on Scanpor tape were used for more than 95% of the tests.

Between 2012 and 2016, a total of 60,995 patients underwent patch testing in the member departments of the IVDK. Of these patients, 2,011 had venous leg ulcers, stasis dermatitis and/or contact dermatitis associated with CVI. These patients formed the study group (CVI patients). In order to derive a specific sensitisation spectrum, a control group was defined for comparative purposes. Since 90% of patients in the study group were aged 49–89, and age has significant effects on the sensitisation spectrum to be observed, the control group consisted of patients of the same age group without venous leg ulcers, stasis dermatitis or dermatitis associated with CVI, who underwent patch testing in the IVDK between 2012 and 2016 because of allergic contact dermatitis or to exclude contact allergy in other dermatological diseases. This group consisted of 30,924 patients.

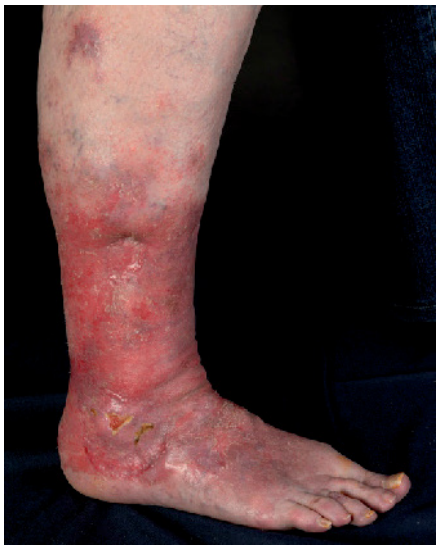

Fig. 1 Allergic contact dermatitis in a venous leg ulcer (photo supplied by the Department of Dermatology, Erlangen University Hospital).

The exact 95% confidence intervals (95% CI) of the reaction rates were calculated for statistical confirmation of the differences in the frequencies of positive reactions to specific allergens in both groups. In the case of non-overlapping 95% CI, a statistical significance at the 5% level is to be assumed.

Results

59% of the study group (2,011 CVI patients) were women and the average age was 72.4 ± 12 years with a median of 75 years. 66% of the control group (30,924 patients aged 49–89 years without CVI) were women and the average age was 62.4 ± 9.5 years with a median of 61 years.

The following DKG test series were used: baseline series (in 1,985 patients = 99% of 2,011), constituents of external (topical) preparations (1,804 patients = 90%), preservatives in topical preparations (1,399 patients = 70%). All other DKG test series were tested in fewer than 30% of the CVI patients. A total of 991 patients (49%) showed at least one positive reaction to an allergen of the DKG test series. In the control group this applied to 13,607 of 30,924 patients (44.0%).

▶ Table 1 lists the 25 allergens to which a positive reaction was most commonly recorded in the study group and their reaction rates. The corresponding reaction rates in the control group are shown for comparison. This table only includes those allergens that were tested in at least 85% of the CVI patients. This is because a lower percentage would suggest that selective testing was performed. In such a case, the more or less strictly applied indication for testing has such a decisive influence on the reaction frequency that it precludes any useful statistical comparison. Based on this limitation, the reactions to methylisothiazolinone (MI) 0.05% aqueous are not included, because although it elicited 3.3% positive reactions (95% CI: 2.5%-4.3%), it was only tested in 83% of the patients. MI was tested in 73% of patients in the control group, of whom 6.1% (5.8%-6.5%) showed a positive reaction.

As 21 of the 25 most common allergens were tested in more than 85% of the patients in both groups, a meaningful comparison is possible. Significantly higher reaction rates to 10 of these allergens were seen in the study group. These consisted of fragrances, constituents of ointment bases and colophony. The most marked differences were observed with tert-butylhydroquinone (10.7% vs. 1.6%), Amerchol L-101 (8.1% vs. 3.1%), lanolin alcohols (7.2% vs. 2.0%) and cetyl stearyl alcohol (4.0% vs. 0.7%). For 7 test preparations, the reaction rates did not differ significantly: fragrance mix, propolis, methyldibromo glutaronitrile, potassium dichromate, ylang-ylang oil, thiuram mix and oil of turpentine. The CVI patients reacted significantly less frequently to 4 allergens than the control group, namely to nickel sulfate, methylchloroisothiazolinone/methylisothiazolinone (MCI/ MI), cobalt chloride and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). Four allergens from the range of ointment bases were tested only selectively, i.e. more or less on a targeted basis, in the control group. Nevertheless, 3 of these 4 allergens caused higher reaction rates in the study group: propylene glycol (4.1% vs. 1.4%), cocamidopropyl betaine (3.6% vs. 2.4%) and butylhydroxyanisole (1.9% vs. 0.3%).

Tab. 1
Rates of reaction to the 25 allergens most commonly tested as positive in the study group. Aqu. = water (aqua); CVI = chronic venous insufficiency; pet. = petrolatum; 95% CI = 95% confidence interval; *Allergen was only tested selectively in the control group, so that a comparison of the reaction rates is not meaningful.

Allergen	Test concentration, vehicle	Study group (2,011 CVI patients) percent positive reactions [95% CI]	Control group (30,924 patients without CVI) percent positive reactions [95% CI]
Peru balsam	25% pet.	13.6 [12.1 – 15.2]	9.8 [9.4 – 10.1]
Fragrance mix	8% pet.	11.7 [10.3 – 13.2]	10.9 [10.5 – 11.3]
tert-Butylhydroquinone	1% pet.	10.7 [9.3 – 12.2]	1.6 [1.4 – 1.8]
Fragrance mix II	14% pet.	8.0 [6.9 – 9.3]	5.9 [5.6 – 6.2]
Amerchol L-101	50% pet.	8.1 [6.8 – 9.4]	3.1 [2.9 – 3.4]
Lanolin alcohols	30 % pet.	7.2 [6.1 – 8.5]	2.0 [1.8 – 2.2]
Colophony	20% pet.	5.3 [4.3 – 6.4]	3.9 [3.7 – 4.2]
Nickel sulfate	5% pet.	5.3 [4.4 – 6.4]	13.4 [13.0 – 13.8]
Propolis	10% pet.	4.2 [3.3 – 5.1]	4.4 [4.2 – 4.7]
Cetyl stearyl alcohol	20% pet.	4.0 [3.1 – 4.9]	0.7 [0.6 – 0.8]
Propylene glycol*	20 % Aqu.	4.1 [3.2 – 5.1]	1.2 [1.1 – 1.4]
Methyldibromo Glutaronitrile	0.2% pet.	3.2 [2.4 – 4.1]	2.9 [2.7 – 3.1]
Jasmine absolute	5% pet.	3.3 [2.5 – 4.2]	1.5 [1.4 – 1.7]
Cocamidopropyl betaine*	1% Aqu.	3.6 [2.8 – 4.5]	2.4 [2.2 – 2.7]
Potassium dichromate	0.5% pet.	3.2 [2.5 – 4.1]	4.0 [3.7 – 4.2]
Ylang-ylang (I+II) oil	10% pet.	3.1 [2.4 – 4.0]	2.8 [2.6 – 3.0]
Methychloroisothiazolinone / Methylisothiazolinone (MCI/MI)	0.01% Aqu.	2.8 [2.1 – 3.7]	5.1 [4.8 – 5.3]
Thiuram mix	1% pet.	2.3 [1.6 – 3.0]	2.3 [2.1 – 2.5]
Cobalt chloride	1% pet.	2.2 [1.6 – 3.0]	4.3 [4.0 – 4.5]
Octyl gallate*	0.3% pet.	2.4 [1.7 – 3.2]	2.3 [2.0 – 2.5]
Sandalwood oil	10% pet.	2.0 [1.4 – 2.7]	1.2 [1.1 – 1.3]
Butylhydroxyanisole (BHA)*	2% pet.	1.9 [1.3 – 2.6]	0.3 [0.2 – 0.4]
Paraben mix	16% pet.	1.5 [1.0 – 2.2]	0.6 [0.5 – 0.7]
Oil of turpentine	10% pet.	1.5 [1.0 – 2.1]	1.2 [1.0 – 1.3]
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC)	5% pet.	1.4 [0.9 – 2.0]	2.3 [2.1 – 2.5]

Discussion

A recently published analysis of IVDK data showed a significant decrease in the frequency of allergic contact dermatitis in CVI patients with venous leg ulcers and stasis dermatitis from 25.9% in the period 1994–2003 to 16.9% in the years 2004–2013 (16.9%), but the allergen spectrum was essentially unchanged (4). In the more recent data evaluation presented here, we also found a qualitatively unchanged allergen spectrum (however with a partial overlap of the evaluation periods). The intention of the present paper was not to reproduce the differentiated and detailed analysis of data in terms of epidemiology in the cited publication, but to present the current spectrum of allergens and evaluate their significance in relation to the skin care of the affected patients.

Peru balsam

Peru balsam led the "hit list" of the most common allergens, with corresponding sensitisations occurring significantly more frequently than in the control group. Peru balsam (INCI: Myroxylon pereirae), the secretion obtained from the cut bark of the Peru balsam tree that grows in Central America, is valued for its action in promoting granulation and wound-healing, but has a considerable sensitising potential. Peru balsam contains more than 250 different components, of which at least 20 are known to be contact allergens, including cinnamic alcohol, eugenol and isoeugenol, which are also present in the fragrance mix. Fifteen constituents of Peru balsam are also found in propolis, including benzoic acid, benzyl alcohol, benzyl cinnamate, coniferyl benzoate, farnesol, vanillin and cinnamic acid. This explains why many patients are simultaneously allergic to Peru balsam and propolis. Not all the known sensitising constituents of Peru balsam are available as individual test substances (7, 8).

Ointment base constituents

There is a notably high rate of allergic reactions to tert-butylhydroquinone (INCI: TBHQ), used as an antioxidant in cos-

metics and skin care products at concentrations of 0.1–1%. The substance is also approved for use in foodstuffs (Additive No. E 319). Compared with data from the years 1994/1995, the sensitisation rate in CVI patients is slightly increased (3). We do not know whether this is due to the increased use of tert-butylhydroquinone in skin care products.

Wool alcohols (INCI: lanolin alcohols) are a mixture of organic alcohols obtained from wool fat (lanolin). Amerchol L101 is a commercial product that contains liquid paraffin as well as lanolin alcohols (9). Lanolin alcohols that are used as an ointment base and emulsifier can undoubtedly cause sensitisation. However, it is questionable whether every positive reaction to the test preparation lanolin alcohols 30% Vas. – or to an even greater degree – to Amerchol L 101 50% Vas., is really indicative of sensitisation because these test preparations can easily cause skin irritation and lead to false-positive and lead to false-positive reactions (10). In addition, there are major differences between the various lanolin alcohol mixtures, so that it is possible for a patient to react positively in the patch test, but to tolerate the (lanolin alcohol-containing) product he or she uses, or vice-versa (11). Finally, patients with stasis dermatitis, for example, can show allergic reactions to lanolin alcohols in the region of already damaged skin, whereas they tolerate them when applied to intact skin in other regions of the body. This phenomenon, known as the "Lanolin Paradox", has been described in the scientific literature (12).

Cetyl stearyl alcohol (INCI: cetearyl alcohol) is another mixture, namely of cetyl alcohol (hexadecanol) and stearyl alcohol (octadecanol) used as an ointment base and/or emulsifier. The test preparation is far less irritant and therefore more reliable for diagnostic purposes. Generally a rare allergen, it apparently plays a more significant role as a sensitiser in CVI patients (3, 4, 9).Propylene glycol (INCI: propylene glycol) caused positive reactions considerably more frequently in the study group than in the control group, although the substance was presumably tested more selectively in the control group. The test preparation propylene glycol 20% Aqu. used by the DKG has a certain irritant potential, so that false-positive reactions can occur (10). However it would not be immediately obvious why this should more often be the case in CVI patients than in the other patients. It is to be assumed that CVI patients are indeed sensitised more frequently to propylene glycol, which is used in topical preparations to adjust viscosity and to retain moisture.

Whereas the antioxidant octyl gallate (INCI: ethylhexyl gallate) appears not to sensitise CVI patients significantly more frequently than the control group, such a tendency is likewise detected with butyl hydroxyanisole (INCI: BHA) which is also used as an antioxidant. The reaction rate to BHA was considerably higher in the study group than in the control group, although it was also probably tested selectively in the latter group. The test preparation octyl gallate 0.3% Vas. is – as is the case with propylene glycol 20% Aqu. – burdened with the label "problem allergen", with many questionable, irritant or false-positive reactions (10), which is not the case with BHA 2% Vas.

Colophony

Chemically modified colophony is contained, for example, in hydrocolloid dressings used on chronic wounds, ulcers etc. (4, 13). This probably represents an important allergen source for the sensitisation to colophony seen in CVI patients, which was found to be slightly more frequent in CVI patients than in the control group. However, one must assume that there is some under-reporting because not all sensitisations to chemically modified colophony are diagnosed with the standardised test substance colophony. In an earlier investigation, approx. 19% of patients with contact allergy to modified colophony did not react to the standard test substance (13).

Parabens

A paraben mix (16% Vas.) is included in the patch test baseline series of the DKG that contains four parabens in concentrations well above the highest concentration permitted for cosmetics and body care products according to the EU Directive on Cosmetics (14). Apparently this high concentration causes irritation, because closer analysis showed that up to 50% of the positive reactions are false-positive and poorly reproducible (15). If these are subtracted from the already low reaction rates, then parabens must be considered not to be significant allergens. Nevertheless, clinically relevant contact allergy to parabens can occur in patients with stasis dermatitis in particular. Fisher described the so-called "Paraben paradox" in 1973: many patients showed an allergic reaction in a skin region that was already damaged, such as in stasis dermatitis, whereas they tolerated parabens in other body areas where the skin was intact (16). Clinical experience confirms this observation.

Other allergens

Quite a number of fragrances are also among the most frequent allergens in the study group. An increased rate of reactions to them compared with the control group was only partly observed. Remarkably, no increased rates of sensitisation to additional preservatives such as methyldibromo glutaronitrile, MCI/MI or MI were found.

Conclusions for everyday practice

Patients with venous leg ulcers and/or stasis dermatitis associated with CVI are frequently sensitized to Peru balsam, ointment bases, especially lanolin alcohols, antioxidants, particularly tert-butylhydroquinone, colophony, fragrances and parabens. Therefore fragrance-free and paraben-free products without Peru balsam (Myroxylon pereirae), lanolin alcohols (lanolin alcohols) and tert-butylhydroquinone (TBHQ) are recommended for skin care in this special group of patients. In view of the sensitisation spectrum presented in this article (and long-known), it is inexplicable why a product advertised for skin care such as Peru-Lenicet® that – with Peru balsam, lanolin and colophony – contains no less than three of the most frequent allergens of CVI patients, is still on the market.

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Conflict of interests

J. Geier and V. Mahler declare no conflicts of interest. C. Erfurt-Berge has received travelling expenses and lecture fees from BSN Medical GmbH, Lohmann & Rauscher GmbH & Co.KG, Smith & Nephew and Urgo GmbH.

Ethical guidelines

Preparation of this manuscript involved no studies in humans or animals.

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